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Evaluation of placental function in women on antiepileptic drugs

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1 Introduction

Placental function may be assessed in high-risk pregnancies by serum human placental lactogen (HPL), serum estriol and urinary estriol excretion. The results of these tests may be influenced by maternal smoking [16] or drugs, such as corticosteroids [6], ampicillin [18], erythromycin [7] and mandelamine [10]. However, for most drugs used by pregnant women little or nothing is known as to whether or not they affect placental function or its biochemical tests.

Antiepileptic drugs are powerful inducers of hepatic microsomal enzyme systems [17] and may alter the metabolism of endogeneous steroid hormones [17] as well as interfere with oral contraception [2]. There is a reason to expect effects on placental function or on its biochemical tests, too, particularly on the metabolism of estriol.

The present study is a systematic evaluation of the placental function in epileptic women, most of whom took antiepileptic drugs throughout their pregnancies.

2 Patients and methods

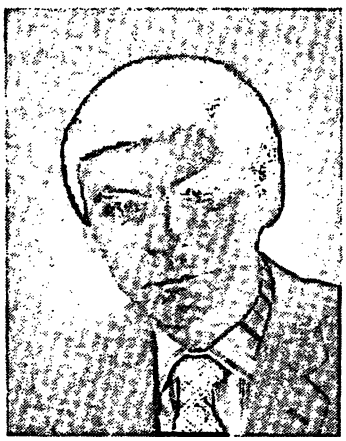
2.1 Patients

A prospective study on 144 consecutive singleton pregnancies of more than 32 weeks duration in 134 women with epilepsy was carried out in 1976–79. The patients were seen fortnightly between 32 to 36 weeks of pregnancy, and weekly thereafter.

2.2 Controls

After the delivery by each epileptic, one control pair (mother and child) was obtained at the same clinic. A control was selected to be the following parturient who fulfilled the chosen matching criteria, namely maternal age ± 3 years, same parity, same fetal sex, and same social class as determined by the mother's profession using the

Curriculum vitae



VILHO K. HIILESMAA *was born in 1943. He studied medicine at Helsinki University and graduated in 1968 after which he entered general practice working at health centres in the surroundings of Helsinki until 1975. From 1975 to 1979, he specialised in obstetrics and gynecology at the Second Department of Obstetrics and Gynecology of Helsinki University. In 1979, he obtained the degree of specialist in Obstetrics and Gynecology and works now as a staff member at the Department. The special research interest is epilepsy and pregnancy which was the theme of his doctoral thesis in 1982.*

Tab. I. Characteristics of the epileptic patients and the matched controls.

	Epileptics N = 144	Controls N = 144
Age*, years; mean ± SD	27.0 ± 4.7	27.0 ± 4.6
Parity*, % first delivery	68%	68%
Smoker, %	24%	27%
Gestational length, days; mean ± SD	276 ± 13	277 ± 12
Fetal sex*, % boys	53%	53%
Placental weight, grams; mean ± SD	632 ± 122	638 ± 125
Birth weight, grams; mean ± SD	3392 ± 496	3430 ± 488

* Matched variable N.S.

standard four-step classification of the Helsinki City Bureau of Statistics. The controls thus represented the general parturient population at the clinic during the study period matched for the chosen parameters. Characteristics of the epileptics and their controls appear in Tab. I.

2.3 Criteria for possible drug effects

"Placental function" was evaluated by serum HPL, 24-hour urinary total estriol excretion, placental weight and birth weight. The possible effects of antiepileptic drugs on placental function were expected to appear in the following three ways. First, as differences between epileptics and controls; second, as differences among epileptics grouped by the type of their treatment; and third, as correlations (positive or negative) between the serum levels of antiepileptic drugs and the placental variables.

The power of the present study was estimated [12] as 90% to detect a difference of 50 grams (i.e. 40% of the standard deviation) in the mean weight of the placenta between women on antiepileptic drugs and the controls at a p-level of 0.05.

2.4 Measurements

Serum concentrations of phenytoin, phenobarbitone, primidone and valproate were measured by gas chromatography [13, 15]. Carbamazepine was assessed by spectrophotometry [11]. Total urinary 24-hour estriol excretion was measured by radioimmunoassay [1] and serum HPL by the commercially available Pharmacia kit which is based on the method of LETCHWORTH [14].

2.5 Calculations and statistics

A computer with BMDP-81 statistical programs [9] was used. Geometric means of available values of HPL and estriol were calculated separately for the 9th month (33rd to 36th week) and the 10th month (37th to 40th week) of pregnancy in each patient.

Skewness of the distributions of urinary estriol, serum HPL and antiepileptic drug levels was correctable by logarithmic or power transformations which allowed standard parametric statistical test.

Differences in placental function variables among the epileptics grouped by the type of their treatment were tested by one-way analysis of variance. Correlations between the serum levels of antiepileptic drugs and the placental variables were measured by the standard product-moment correlation coefficients. To cope with the spurious correlations expected among the 21 tests of correlation to be performed, a level of significance of $\frac{0.05}{21} = 0.0023$ was required for any one correlation before considering it genuine [3].

Tab. II. Serum HPL and total urinary 24-h estriol excretion in epileptic women during late pregnancy.

	Month of pregnancy	Epileptic patients			Reference for normal
		No.	Median	2.5th to 97.5th centile range	2.5th to 97.5th centile range
HPL (mg/l)	9th	102	7.3	3.4– 11.8	3.0– 12.0
	10th	92	7.6	3.6– 12.9	3.5– 12.5
Estriol (μmol/24-h)	9th	58	47	20 – 90	24 – 86
	10th	107	70	32 –134	35 –125

Tab. III. Analysis of variance of Placental variables in epileptic patients grouped according to their regimen*.

		log-serum HPL		log-urinary estriol		Placental weight		Birth weight
		9th mo.	10th mo.	9th mo.	10th mo.	absolute	% of birth weight	
No. of patients		104	94	60	110	144	144	144
One-way analysis	F	1.0	0.4	1.0	0.2	1.8	2.3	0.5
of variance	p	0.4	0.8	0.4	0.9	0.1	0.06	0.7

* The 144 epileptic patients were classified as follows: Phenytoin monotherapy (N = 55); carbamazepine monotherapy (20); combinations including phenobarbitone (26); other combinations (24); and patients not on antiepileptic drugs (18).
F = F-value. P = probability for occurrence of differences at least as large as those observed among the five groups.

3 Results

No significant differences between the epileptic mothers and the controls were seen with regard to gestational age, placental weight and birth weight (Tab. I). The levels of serum HPL and total urinary 24-hour estriol excretion of women with epilepsy agreed well with the references (Tab. II). No notable differences in the serum HPL, urinary estriol, placental weight or birth weight were observed among the epileptics grouped by their drug regimen (Tab. III).

Serum levels of antiepileptic drugs in late pregnancy were often below the "therapeutic" ranges [8] (Tab. IV). None of the coefficients of correlation between drug levels and serum HPL, urinary estriol, placental weight and birth weight reached the pre-established limit of $p = 0.0023$ (Tab. V). The positive correlation between serum phenytoin and birthweight ($r = 0.25$; $p = 0.015$) was reduced after an adjustment for gestational age and sex.

Values below the 2.5th percentile of HPL (in 3 patients) and estriol (in 7) appeared associated with pre-eclampsia and intrauterine growth retardation but not with maternal antiepileptic treatment.

The incidences of pregnancy complications among the 144 epileptics and 144 controls (in parenthesis) were similar: pregnancy-induced hypertension 8% (10%); albuminuria 3% (3%); intrauterine growth retardation, defined as birth weight below the 10th percentile of the Helsinki standard, 9% (8%); placental abruption 1% (1%).

4 Discussion

No genuine associations between the types or serum levels of the antiepileptic drugs and serum HPL, urinary estriol excretion, placental weight and birth weight were observed in the present

Tab. IV. Serum levels of antiepileptic drugs in the third trimester of pregnancy

Drug	Number of patients		Serum level µmol/l		Therapeutic range µmol
	users of the drug	with levels measured	Median	Range	
Phenytoin	104	95	18	1– 70	20– 80
Carbamazepine	41	40	21	5– 45	17– 40
Phenobarbitone	26	26	31	2–101	60–110
Valproic acid	9	7	164	133–353	350–900
Primidone	5	5	22	11– 31	20– 70
Clonazepam	5	..	..	..	..
Ethosuximide	2	..	..	..	..
Diazepam	2	..	..	..	..
No drugs	18	..	..	..	..

Levels are medians for 33 to 40th week of pregnancy.

Tab. V. Correlations between serum levels of antiepileptic drugs and placental variables

Drug		Serum HPL		Urinary estriol		Placental weight		Birth weight
		9th mo.	10th mo.	9th mo.	10th mo.	absolute	% of birth weight	
Phenytoin	No.	70	66	36	77	95	95	95
	r	−0.05	−0.02	−0.30	−0.20	0.10	−0.09	0.25
	p	0.7	0.9	0.08	0.08	0.3	0.4	0.015
Carbamazepine	No.	35	27	21	32	40	40	40
	r	−0.16	0.27	0.24	−0.22	0.03	0.18	0.03
	p	0.4	0.2	0.3	0.2	0.8	0.3	0.8
Phenobarbitone	No.	21	19	11	24	26	26	26
	r	0.01	−0.08	−0.24	−0.26	0.02	0.10	0.08
	p	0.8	0.7	0.5	0.2	0.9	0.6	0.7

Transformations prior to analysis: Logarithm of HPL and oestriol; square root of phenytoin and phenobarbitone.
r = product-moment correlation coefficient.
p = two-tailed probability for a coefficient at least as large as observed.

study. This accords with the only similar series previously reported [5]. The inherent variability of HPL and estriol is large, and small changes may remain undetected when the study sample is relatively small.

An exigent level of significance was required before considering any of the observed differences genuine. This was necessary because of the large number of statistical tests performed. In such a situation some sporadic associations are to be expected, and the concentional general level of $p < 0.05$ is no more valid [3].

The epileptic patients in the present study seldom showed very high serum levels of antiepileptic drugs. The possibility that higher than therapeutic concentrations of antiepileptic drugs might affect placental function cannot thus be excluded.

While long-term use of antiepileptic drugs appears to have little, if any, clinically important effects on placental function or on its biochemical tests, short-term use of phenobarbitone in pre-eclamptic patients may lower serum estriol [4].

Although the present study showed no change in the total urinary 24-hour estriol excretion, it does not exclude induction by the drugs in the metabolism of estriol, such as alterations in the various glucuronide and sulphate conjugates of estriol.

Out-of-range values of placental function tests in epileptic mothers should evidently not be considered harmless biochemical anomalies due to the mother's medication as is the case e.g. for ampicillin [18]. Serum HPL and 24-hour total urinary estriol can be used in the usual manner to assess fetoplacental function in epileptic women who are on long-term treatment with phenytoin, phenobarbitone or carbamazepine in spite of the powerful enzyme induction properties of the drugs.

Summary

Placental function in the presence of antiepileptic drugs was assessed in 144 unselected late pregnancies of women with epilepsy. The most common drugs of the mothers were phenytoin (104 pregnancies), carbamazepine (42) and phenobarbitone (26). 144 control parturients matched for maternal age, parity, fetal sex and social class were also studied.

No significant associations between the types or the serum concentrations of the mother's antiepileptic drugs and her serum HPL, 24-hour total urinary estriol excretion, placental weight or her child's birth weight were observed. However, since the serum levels of antiepileptic drugs were usually within or below the therapeutic ranges the study does not exclude the possibility that very high drug concentrations might have some effects.

The incidences of common pregnancy complications did not differ between epileptics and controls. Serum HPL and urinary estriol values in epileptic women agreed well with the references for normal.

It is concluded that the long-term use of antiepileptic drugs during pregnancy has no clinically important effects on placental function or on its biochemical tests in spite of the enzyme induction properties of these drugs. Values of serum HPL and 24-hour total urinary estriol excretion can thus be interpreted in the usual manner in women who are on antiepileptic medication.

Keywords: Antiepileptic drugs, epilepsy, estriol, human placental lactogen, placental function tests, pregnancy.

Zusammenfassung

Bestimmung der Plazentafunktion bei Frauen unter antiepileptischer Therapie
Wir untersuchten die Plazentafunktion bei 144 zufällig ausgewählten Frauen unter antiepileptischer Medikation in der Spätschwangerschaft. Die am häufigsten verabreichten Medikamente waren Phenytoin (104 Fälle), Carbamazepin (42 Fälle) und Phenobarbital (26 Fälle). Als Kontrollgruppe untersuchten wir 144 Schwangere, die bezüglich des mütterlichen Alters, der Anzahl der Geburten, des fetalen Geschlechts und der sozialen Herkunft mit den Patientinnen unseres Untersuchungskollektivs vergleichbar waren und ihnen zugeordnet wurden.
Es fand sich kein signifikanter Zusammenhang zwischen dem Typ der pharmakologischen Verbindung bzw. ihrer Serumkonzentration und dem HPL-Wert im Serum, der Östriol-Ausscheidung im 24-Stunden-Urin, dem Plazentagewicht oder dem kindlichen Geburtsgewicht. Die Serumkonzentrationen der Antiepileptika lagen jedoch immer innerhalb oder sogar unterhalb des therapeutischen Bereichs. Daher können wir nicht ausschließen, daß sehr hohe Konzentrationen möglicherweise andere Effekte haben.
Gewöhnliche Schwangerschaftskomplikationen traten bei der Kontrollgruppe und bei den epileptischen Schwangeren gleich häufig auf. Die HPL-Werte im Serum und die Östriol-Ausscheidung im Urin zeigten eine gute Übereinstimmung mit den als normal eingestuften Referenzwerten.
Wir schließen aus unserer Untersuchung, daß eine **antiepileptische Langzeitmedikation während der Schwangerschaft keinen klinisch bedeutsamen Einfluß auf die Plazentafunktion** bzw. ihre biochemische Bestimmung hat, obwohl die Antiepileptika enzyminduzierende Eigenschaften haben. Die Serum-HPL-Werte und die Ausscheidung im 24-Stunden-Urin können daher unter antiepileptischer Therapie wie sonst üblich interpretiert werden.

Schlüsselwörter: Antiepileptika, Epilepsie, Human placental lactogen (HPL), Östriol, Plazentafunktionstests, Schwangerschaft.

Résumé

Evaluation de la fonction placentaire chez les femmes sous traitement anti-épileptique
La fonction placentaire en cours de traitement anti-épileptique a été étudiée en fin de grossesse chez 144 femmes épileptiques non sélctionnées. Phenytoine (104 grossesses), carbamazepine (42) et phenobarbital (26) sont les médicaments les plus utilisés. 144 femmes enceintes témoins apparieées pour l'âge maternel, la parité, le sexe du foetus et la classe sociale ont été également étudiées.
Il n'a pas été mis en évidence de corrélation significative entre le type de médicament anti-épileptique pris par la femme et sa concentration sérique avec l'HPL sérique, l'estriol urinaire total des 24 heures, le poids placentaire ou le poids de naissance du nouveauné. Toutefois, dans la mesure où les taux sériques des médicaments anti-épileptiques se situent au niveau ou en-dessous des taux thérapeutiques, l'étude n'exclut pas la possibilité que des concentrations élevées puissent entrainer certains effets.
L'incidence des complications habituelles de la grossesse ne diffère pas chez les patientes épileptiques et chez les témoins. Les valeurs de l'HPL sérique et de l'estriol urinaire chez les épileptiques sont conformes aux taux considérés comme normaux.
Les auteurs concluent que la prise au **long cours d'anti-épileptiques pendant la grossesse n'a pas d'effet important en pratique clinique sur la fonction placentaire** ou sur ses tests biochimiques malgré l'action d'induction enzymatique de ces médicaments. Chez les patientes qui prennent des anti-épileptiques, les valeurs de l'HPL sérique et de l'estriol urinaire total des 24 heures peuvent être interprétées comme d'habitude.

Mots-clés: Anti-épileptiques, épilepsie, estriol, grossesse, hormone lactogène placentaire, tests de fonction placentaire.

Bibliography

[1] ANDERSON, D. W., U. GOEBELSMANN: Rapid radioimmunoassay of total urinary estriol. Clin. Chem. 22 (1976) 611
[2] ANONYMOUS: Drug interaction with oral contraceptive steroids. Brit. Med. J. 281 (1980) 93
[3] ANONYMOUS: Illegal fishing. Lancet II (1981) 1268
[4] BASALAMAH, A. H., M. J. HARDY: Phenobarbitone and serum unconjugated oestriol concentrations in four pregnant women with hypertension. Brit. Med. J. 281 (1980) 272
[5] BATTINO, D., L. BOSSI, M. CANGER, M. L. COMO, M. DE GIAMBATTISTA, A. OLDRINI, G. PARDI, G. PIFAROTTI: Obstetrical monitoring of pregnancy

in 59 patients with epilepsy. In: JANZ, D., M. DAM, A. RICHENS, L. BOSSI, H. HELGE, D. SCHMIDT (eds.): Epilepsy, pregnancy and the child. Raven Press, New York 1982

[6] BROWN, J. B., N. A. BEISCHER, M. A. SMITH: Excretion of urinary oestrogens in pregnant patients treated with cortisone and its analogues. J. Obstet. Gynaecol. Brit. Cwlth. 75 (1968) 819

[7] CALLAGHER, J. C., M. A. ISMAIL, S. ALADJEM: Reduced urinary estriol levels with erythromycin therapy. Obstet. and Gynec. 56 (1980) 381

[8] DEOM, A., J. M. AESCHLIMANN, A. AELLIG: Conversion scales for commonly requested serum concentrations of drugs and other substances of therapeutic and toxicological importance, and of hormones. Lancet II (1980) 1241

[9] DIXON, W. J.: BMDP statistical software. University of California press, Los Angeles 1981

[10] ERAZ, J., R. HAUSKNECHT: Diminished urinary estriol due to mandelamine administration during pregnancy. Amer. J. Obstet. Gynec. 104 (1969) 924

[11] FREY, H., T. YRJÄNÄ: Carbamazepine titers in epileptic patients. Scand. J. Clin. Lab. Invest. Suppl. 113, 25 (1970) 90

[12] GORE, S. M., D. G. ALTMAN: Statistics in practice. British Medical Association, London 1982

[13] KUPFERBERG, H. J.: Quantitative estimation of diphenylhydantoin, primidone and phenobarbital by gas-liquid chromatography. Clin. Chim. Acta 29 (1970) 283

[14] LETCHWORTH, A. T., R. BOARDMAN, C. BRISTOW, J. LANDON, T. CHARD: Rapid radioimmunoassay for HCS. J. Obstet. Gynaec. Brit. Cwlth. 78 (1971) 535

[15] MEIJER, J. W. A., I. HESSING-BRAND: Determination of lower fatty acids, particularly of the antiepileptic dipropylacetic acid, in biological materials by means of microdiffusion and gaschromatography. Clin. Chim. Acta 42 (1973) 215

[16] MOSER, R. J., D. R. HOLLINGSWORTH, J. W. CARLSON, L. LAMOTTE: Human chorionic somatomammotropin in normal adolescent primiparous pregnancy. I. Effect of smoking. Amer. J. Obstet. Gynec. 120 (1974) 1080

[17] RICHENS, A.: Liver enzyme induction by antiepileptic drugs: its clinical significance. In: RICHENS, A., F. P. WOODFORD (eds.): Anticonvulsant drugs and enzyme induction. Elsevier, North-Holland 1976

[18] WILLMAN, K., M. O. PULKKINEN: Reduced maternal plasma and urinary estriol during ampicillin treatment. Amer. J. Obstet. Gynec. 109 (1971) 893

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